U.S. DEPARTMENT OF COMMERCE; PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 32286R006

U.S. APPLICATION NO. (if known, see 37 CFR 1.5): 09/786057

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/BR99/00072	3 September 1999	8 September 1998

TITLE OF INVENTION
PROCESS AND COMPOSITION FOR ENHANCING THE ACTION OF VITAMIN A ON THE CELLULAR ACTIVITY OF AN INDIVIDUAL, AND USE OF VITAMIN C

APPLICANT(S) FOR DO/EO/US --- Roberto Alcantara Martins Zucchetti, et. al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. □ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. ■ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ■ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
a. ■ is transmitted herewith (required only if not transmitted by the International Bureau)b □ has been transmitted by the International Bureau (see Form 308) c. □ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. □ A translation of the International Application into English (35 U.S.C. 371(c)(2))

7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
a. □ are transmitted herewith (required only if not transmitted by the International Bureau)
b. □ have been transmitted by the International Bureau.
c. □ have not been made; however, the time limit for making such amendments has NOT expired.
d. ■ have not been made and will not be made.

8. □ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. □ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. □ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. (w/ copy of PTO-1449 and each reference cited therein and Int'l Search Rept)

12. □ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. □ A FIRST preliminary amendment.
□ A SECOND or SUBSEQUENT preliminary amendment.

14. □ A substitute specification.

15. □ A change of power of attorney and/or address letter.

16. ■ Other items or information:

a) PCT Request (Form PCT/RO/101)
b) Notification of Transmittal of the International Search Report or the Declaration (PCT/ISA/220);
c) International Search Report (PCT/ISA/210);
d) Notification of Transmittal of the International Preliminary Examination Report (PCT/IPEA/416);
e) International Preliminary Examination Report (PCT/IPEA/409) **including the amended claim set to be prosecuted;**
f) PCT Publ. WO 00/13659 with Search Report
g) PCT Written Opinion (Form PCT/IPEA/408)

JC02 Rec'd PCT/PTO 01 MAR 200

U.S. DEPARTMENT OF COMMERCE, PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
32286R006

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
09/788057

17. ■ The following fees are submitted:	CALCULATION	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than □ 20 □ 30 months from the earliest claimed priority date (37 CFR 1.495(e)).	$ -	

Claims	Number Filed	Number Extra	Rate		
Total Claims	6 - 20 =	-	x $18.00	$ -	
Independent Claims	1 - 3 =	-	x $80.00	$ -	
Multiple dependent claim(s) (if applicable)			+ $260.00	-	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00	
SUBTOTAL =				$ 860.00	
Processing fee of $130.00 for furnishing the English translation later than □ 20 □ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$ -	
TOTAL NATIONAL FEE =				$ 860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property.			+	$ 0.00	
TOTAL FEES ENCLOSED =				$ 860.00	
				Amount to be refunded	$
				charged	$

a. ■ A check in the amount of $ 860.00 to cover the above fees is enclosed.
b. □ Please charge my Deposit Account No. 02-4300 in the amount of $____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required with respect to any deficiency in the above noted "Basic National Fee", or credit any overpayment to Deposit Account No. 02-4300 .

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Dennis C. Rodeers - 32,936
NAME REGISTRATION NO.

Date: March 1, 2001

Title: "PROCESS AND COMPOSITION FOR ENHANCING THE ACTION OF VITAMIN A ON THE CELLULAR ACTIVITY OF AN INDIVIDUAL, AND USE OF VITAMIN C"

Field of the Invention

The present invention refers to a process for improving the effects of Vitamin A used in cosmetic compositions in order to enhance the cellular activity of an individual.

Background of the Invention

The compound generically known as Vitamin A comprises retinol and its derivatives, also known as retinoids, in addition to its acidic or aldehyde form, respectively retinoic acid and retinal. Retinoic acid has application in the pharmaceutical and cosmetic industries being, however, prohibited in several countries for cosmetic use due to the adverse effects of irritability which it may cause. Examples of pharmaceutical applications of retinoic acid can be found in the article "Relationships between structure and activity of retinoids", published by Nature, Volume 236, pages 110-113, of September 9, 1996.

In the cosmetic area Vitamin A is usually employed in the form of retinol or some of its retinoids such as retinyl palmitate, and the use of retinol causes various biologic activities, many of which are highly desirable in cosmetic compositions, particularly in those intended to improve the general conditions of the skin of the individual subjected to the topic use thereof. Results achieved by the topic use of Vitamin A are described in passages contained in pages 82 - 119 of the article entitled "Vitamin A Complex", written by Wade Cheng, PhD and Shirley DePetris and published by Skin Inc., March/April 1998.

Moreover, regulation and balance of the epidermal cellular growth through the total synthesis of collagen, among others, such as retention of water in the skin, are also known as effects resulting from the use of Vitamin A in its pure form, called Retinol.

One problem resulting from the use of Vitamin A, either in its pure form or as a derivative, is that, on the one side it promotes the effects of increasing the cellular activity at the level of the dermis and epidermis, accelerating the process of proliferation and differentiation of the keratinocytes and reorganization of the fibers of the dermis (collagen and elastin). But on the other side it must be administered at low doses due to its toxicity. This fact limits the use of Vitamin A and its derivatives to lower contents or requires the utilization of other means that are able to minimize the discomfort of irritation in the skin.

In fact, the use of retinol at low contents is quite common, as shown by several studies, such as the one conducted by the Hamburg Clinic of Experimental Dermatology, in Germany, which doscloses tests with low contents of Retinol (0.034%) for men and women with age between 22 and 34 years and which show that such a concentration of retinol could reduce the amount and the deepness of wrinkles. Therefore, this study generically shows the effect of reducing wrinkles by the use of low contents of retinol.

On the other hand, what has been observed is that, even though low concentrations of retinol effectively cause little or no irritation, the results on the skin can remain below the desired levels for the present standards of demand of the consumers in view of the small amount of retinol incorporated in the cosmetic composition and available for its biological action.

In this respect, there have been attempts to obtain compositions of Vitamin A that present effective action and do not cause adverse effects, for instance, the irritation of the skin. As an example, documents US 5516793 and US 5703122 in the name of Avon Products, Inc., are incorporated herein as prior art references. These documents describe a generic association of amounts ranging from 0.5 to 25% by weight of Vitamin C with several irritating active principles, among which Vitamin A is included. This association, however, has the exclusive purpose of reducing irritation of the skin caused by Vitamin A.

It is therefore an objective of the present invention to provide an alternative for the use of Vitamin A at such concentrations that enable an increase in its properties which are beneficial to the skin, without presenting the problems cited above.

Summary of the Invention

The present invention refers to a process for enhancing the action of Vitamin A on the cellular activity of an individual comprising the association of Vitamin C with Vitamin

A, which will be applied to the referred-to individual at a weight ratio ranging from about 1:1 to about 10:1.

In another aspect, the invention refers to a composition for enhancing the action of Vitamin A on the cellular activity of an individual comprising Vitamin C in association with Vitamin A at a weight ratio in the range from about 1:1 to 10:1.

The invention further refers to the use of Vitamin C for enhancing the action of Vitamin A on the cellular activity of an individual.

Brief Description of the Drawings

- Figure 1 shows a graph representing the increase obtained in the cellular activity of a reconstituted skin by the synergistic effect of an association of Vitamin C with Vitamin A according to the invention as compared to the cellular activity of a reconstituted skin treated only with pure Vitamin A.

- Figure 2 shows the synergistic effect on the recuperation and the increase in the cellular activity in reconstituted skin treated with Vitamin A associated with Vitamin C when subjected to ultraviolet irradiation.

Detailed Description of the Invention

After detailed studies the inventors have found that the association of Vitamin C added to compositions containing Vitamin A at a weight ratio ranging from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1, provides a surprising increase in the cellular activity effects of Vitamin A on an individual.

"Vitamin C" useful for the present invention comprises Vitamin C in its pure form or its derivatives, namely L-ascorbic acid in its molecular form as well as its salts and esters such as ascorbyl phosphate.

As used herein, the expression "an increase in the cellular activity" means the occurrence of a benefit brought about by the increase or improvement at least in one of the situations selected from the maintenance of the cellular condition, the cellular proliferation and the metabolic activity especially in cutaneous cells.

Tests carried out on reconstituted skin show that a treatment of the skin *in vitro* with the association of Vitamin C with Vitamin A according to the present invention promotes an unexpected synergistic increase in the cellular activity of 100% as compared to the cellular activity observed in the same skin treated exclusively with pure Vitamin A or retinol (figure 1).

In the same surprising way, it has been noted that the association of Vitamin C with Vitamin A promotes reconstitution, recuperation and increase in the cellular activity of the skin, even when the individual is subjected to ultraviolet irradiation, which is recognized to cause deleterious effects on the skin and its cells. Tests carried out to this respect show a synergistic effect of reconstitution and increase in the cellular activity of 5% on reconstituted skin treated with Vitamin A associated with Vitamin C when subjected to ultraviolet irradiation (figure 2).

The association of Vitamin C with Vitamin A according to the present invention may be carried out at the moment of the application of these compounds to the individual, but it can also be advantageously formulated as a cosmetic composition containing the two vitamins at a weight ratio ranging from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1 of Vitamin C to Vitamin A.

According to a preferred embodiment of the invention, said cosmetic composition comprises, by weight, about 0.01 to about 0.9% of Vitamin C and from about 0.008 to about 0.20% of Vitamin A, based on the total weight of the composition. Even more preferably, the composition contains from about 0.02 to about 0.8% by weight of Vitamin C and from about 0.009 to about 0.16% by weight, of Vitamin A and even more preferably the composition contains 0.02 wt.% of Vitamin C and from about 0.009 to about 0.02 wt% Vitamin A, all the percentages based on the total weight of the composition.

It is noted that, even at very low concentrations, Vitamin A associated with Vitamin C as defined in the present invention achieves the desired effects of increase in the cellular activity.

The cosmetic compositions containing Vitamin A and Vitamin C at the proportions cited above can also contain other appropriate additives and formulation aids, such as antioxidants for combating free radicals. Among the useful antioxidants, Vitamin E stands out, both in its pure form presented by di-α-tocopherol, and as its derivatives such as dil-α-tocopherol, or 2,6-di-terc-buthyl-p-cresol (BHT).

The introduction of Vitamins C, A and E in microspheres increases their action and makes it possible for them to reach the deeper layers of the skin with greater, or even total, integrity, without degeneration of the product in the path between the application area and the place of action.

In a particularly preferred way, the cosmetic compositions according to the present invention are formulated in such a manner, that their components are contained in organic vectors such as microspheres and, more particularly, in microspheres or microcapsules containing biologically active material ("Talasferas") such as those defined in US Pat 5,395,620, or in Brazilian patent application PI 9706994-7, filed in the name of this same applicant.

The composition as described above may contain a plurality of said microspheres, in a dispersed form, comprising Vitamin A and, for example, an antioxidant such as Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres. A particularly preferred composition comprises a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005% by weight, and a second group of microspheres containing 0.02% by weight of Vitamin C.

Advantageously, in association to the groups of microspheres previously mentioned, such a composition may further contain, in addition to Vitamin A and Vitamin E, cosmetic compounds selected from the group comprising skin structurers, preferably squalan and sphingolipide complexes, skin micronutrients, preferably seaweed extract, sensorial agents, for example, moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glycol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

In one particular embodiment of the present invention, the composition containing Vitamin A and Vitamin C may be in the form of an emulsion and, in this case, the Vitamin C preferably used is L-ascorbic acid stabilized by hydrogen-bridge-forming compounds. Such processes of stabilizing L-ascorbic acid are described in applications PI 9704418-0 and PI 9704728-7, also filed by this same applicant.

As an illustrative example of another possible embodiment of the present invention, the composition is formulated as a gel in which the weight ratio of Vitamin C to Vitamin A is advantageously about 5:1, Vitamin C being present preferably in amounts of about 0.75% and Vitamin C being present in amounts of about 0.16 wt.%, based on the total weight of the composition. This gel composition may further contain thickeners such as carbopol, fragrances, conservants and water.

Claims

1. Composition for enhancing the action of Vitamin A on the cellular activity of an individual, characterized in that it contains a plurality of dispersed microspheres, said plurality of microspheres comprising Vitamin A and an antioxidant preferably Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres.

2. Composition according to claim 1, characterized in that Vitamin C is present at a composition of about 0,02% by weight, and Vitamin A is present at a concentration of about 0,009% to 0,02% by weight, based on the total weight composition.

3. Composition according to claim 2, characterized in that Vitamin C is contained in the second group of microspheres at a concentration of 0,02%.

4. A composition according to claim 3, characterized in that it contains a first group of microspheres containing Vitamin A at an average concentration of about 0,014% by weight, based on the total weight of the composition.

5. A composition according to claim 4, characterized in that it contains a first group of microspheres containing Vitamin A at an average concentration of 0,014% and Vitamin E at an average concentration of 0,0005% by weight, and cosmetic compounds selected from the group consisting of skin structures, preferably squalan and sphingolipide complexes, micronutrients of the skin , preferably seaweed extract, sensorial agents, preferably moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glycol and cethyl lactate and silicones such as cyclometicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin any soybean lecitin thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

6. A composition according to claim 1 comprising Vitamin C in association with Vitamin A at a weight ration ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

FIG. 1 - Without exposure to radiation

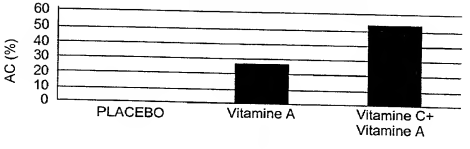
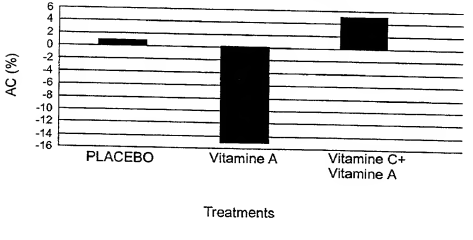


FIG. 2 - With exposure to radiation



UNITED STATES (Form BDW-1)
Patent and Design Patent
Sole & Joint Inventors
Convention & Non-convention
PCT & Non-PCT
This form cannot be amended, altered or changed after it is signed.
(For use only for inventors who understand the English language.)

Declaration and Power of Attorney
United States Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter which is claimed and for which a patent is sought on the invention entitled
"Process and composition for enhancing the action of vitamin A on the cellular activity of an individual, and use of vitamin C" the specification of which
(check one) ☐ is attached hereto.
☐ was filed on March 1, 2001 as U.S. Application Serial No.________ and *(if applicable)* was amended on ________.
☐ was filed as PCT International Application No. PCT/BR99/00072 on September 3,1999 and *(if applicable)* was amended under PCT Article 19 on ________.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and PCT application(s) for patent or inventor's certificate listed in this Declaration and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Foreign/PCT Application No.	Country	Filing Date	Priority Claimed? (yes/no)
PI 9803936-9 PCT/BR99/00072	BR PCT	September 8,1998 September 3, 1999	Yes Yes

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) and PCT International Application(s) listed in this Declaration and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT International filing date of this application:

U.S. Application No.	Filing Date	Status (patented/pending/abandoned?)
PCT/BR99/00072	September 3, 1999	

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Joseph A. DeGrandi (17446), Robert G. Weilacher (20531), Richard G. Young (25638), Michael A. Makuch (32263), Bernard A. Meany (22601), Helen M. McCarthy (31513), Dennis C. Rodgers (32936), William F. Rauchholz (34701), G. Byron Stover (34737), Thomas L. Evans (35805), Maurice U. Cahn (21444), Robert James Worrall (37069), and William J. Bundren (31712).

Send all correspondence to Beveridge, DeGrandi, Weilacher & Young, Suite 800, 1850 M Street, N.W., Washington, D.C. 20036. Facsimiles may be sent to (202) 659-1462. Direct all telephone calls to (202) 659-2811.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Signature: ________ Date: JUN 20th, 2001

BDWY 694 *(Supply similar information and signature for third and subsequent joint inventors.)*

Supplemental Sheet for Declaration and Power of Attorney

(Please use for supplying information and signatures of third and subsequent joint inventors.)

320

Full name of third joint inventor, if any: Luciana Villa Nova Silva
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Signature: Luciana V. Nova Silva Date: 26 jun. 2001

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Signature: _____ Date: _____

Full name of fifth joint inventor, if any:
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Post office address:

Signature: _____ Date: _____

Full name of sixth joint inventor, if any:
Residence *(city, state, country)*: Citizenship:
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Signature: _____ Date: _____

Full name of seventh joint inventor, if any:
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Post office address:

Signature: _____ Date: _____

Full name of eighth joint inventor, if any:
Residence *(city, state, country)*: Citizenship:
Post office address:

Signature: _____ Date: _____

Full name of ninth joint inventor, if any:
Residence *(city, state, country)*: Citizenship:
Post office address:

Signature: _____ Date: _____

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Application deficiencies found during scanning:

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☑ ***Scanned copy is best available.*** Declaration